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(54) Galenical retard formulations

(57) A solid dispersion of a pharmacologically active agent in a crystalline matrix as a carrier is characterized by an agent which

a. has a solubility of maximally 0.01% at 37°C in water,
b. is present in the matrix at a total concentration of more than 5 percent of weight,
c. is present in the matrix at a concentration of above 5 percent by weight in a coherent crystalline form.

The matrix can be a polyalkylene glycol and the active agent may be a dihydropyridine etc.

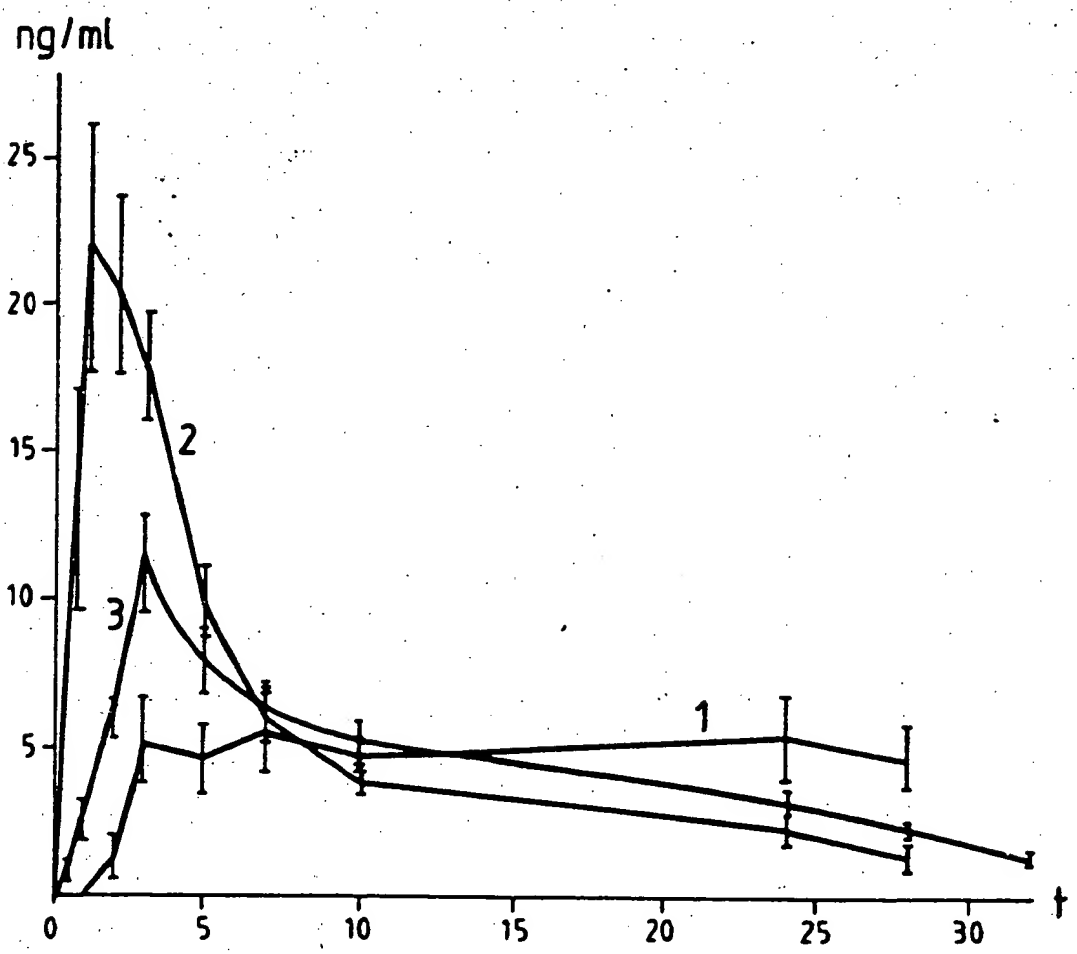

FIG. 1

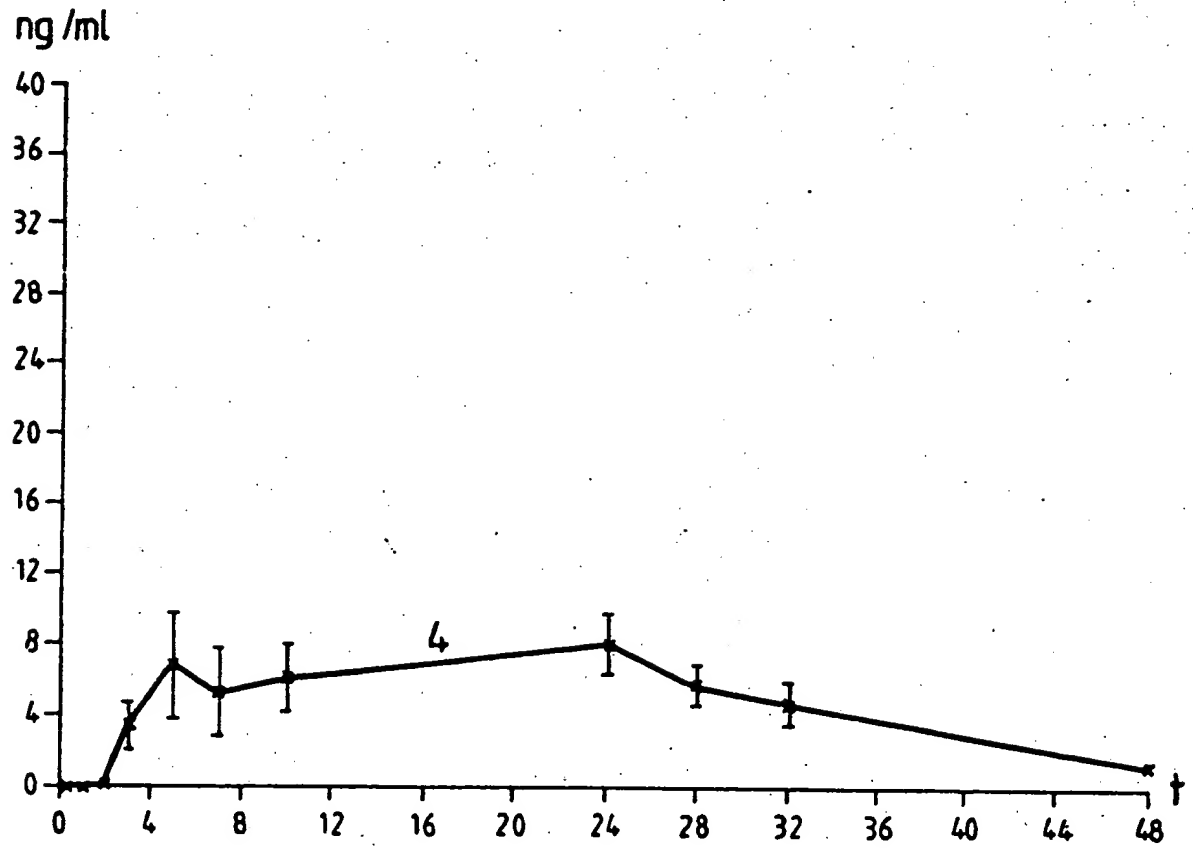

FIG. 2

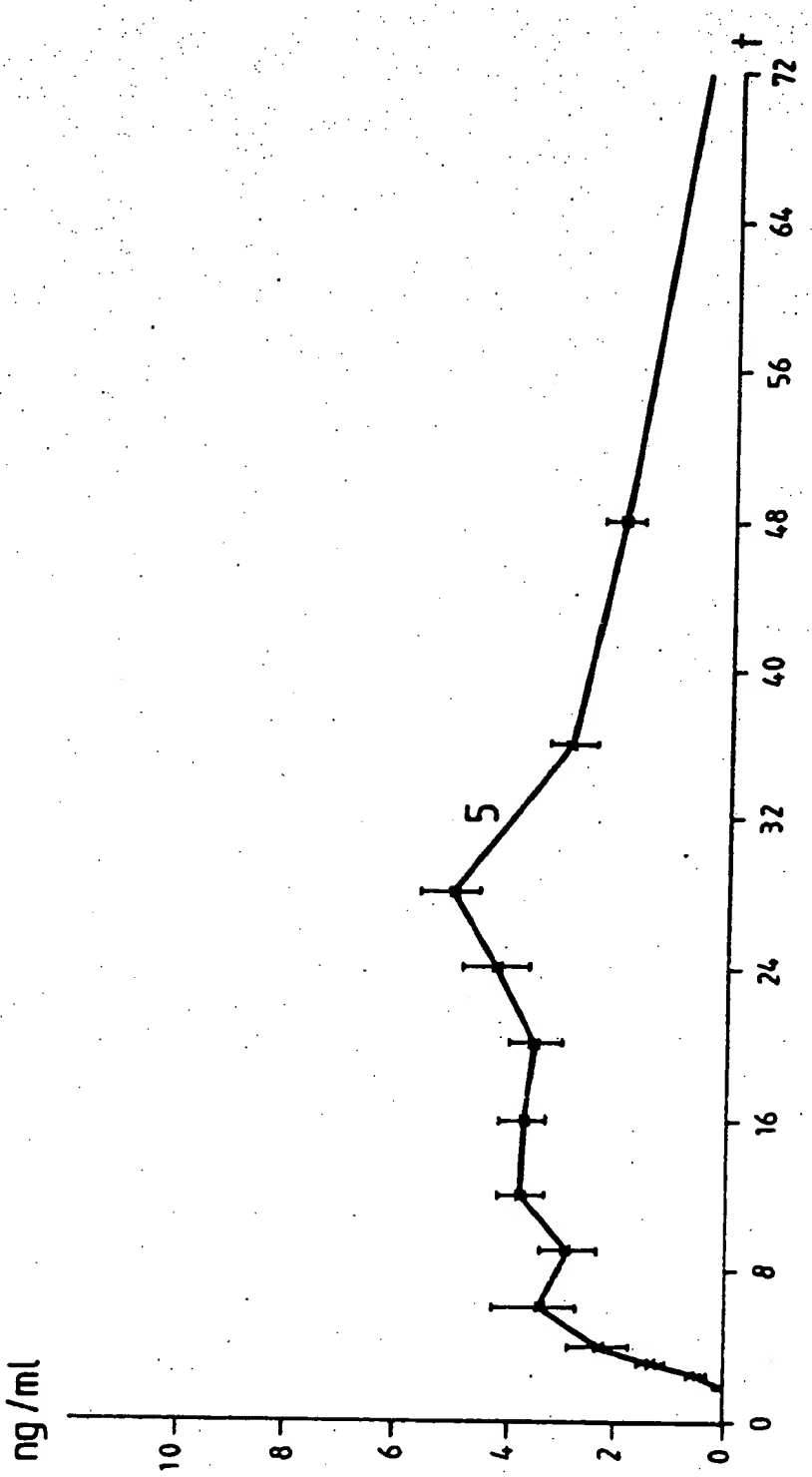

FIG. 3

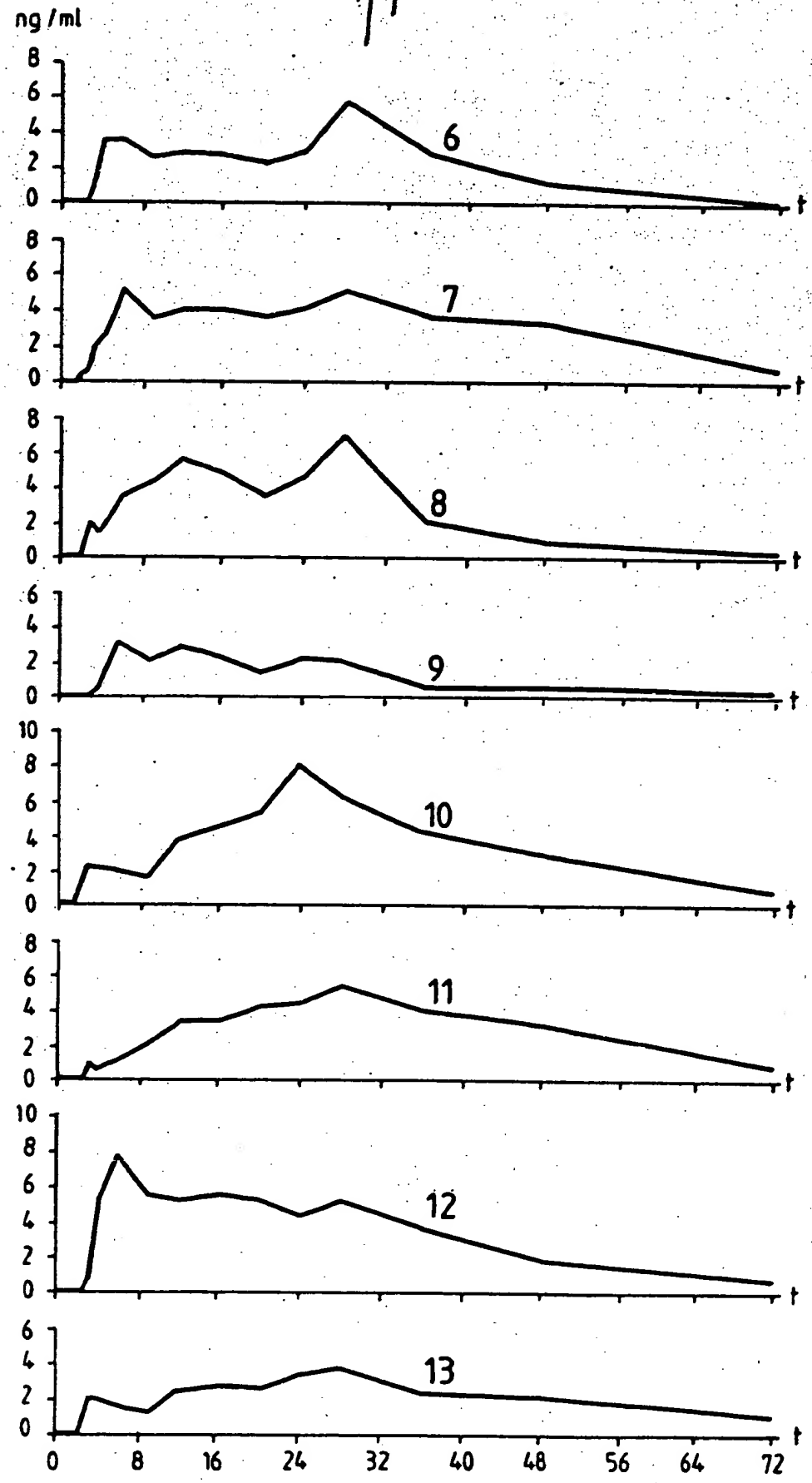

FIG. 4

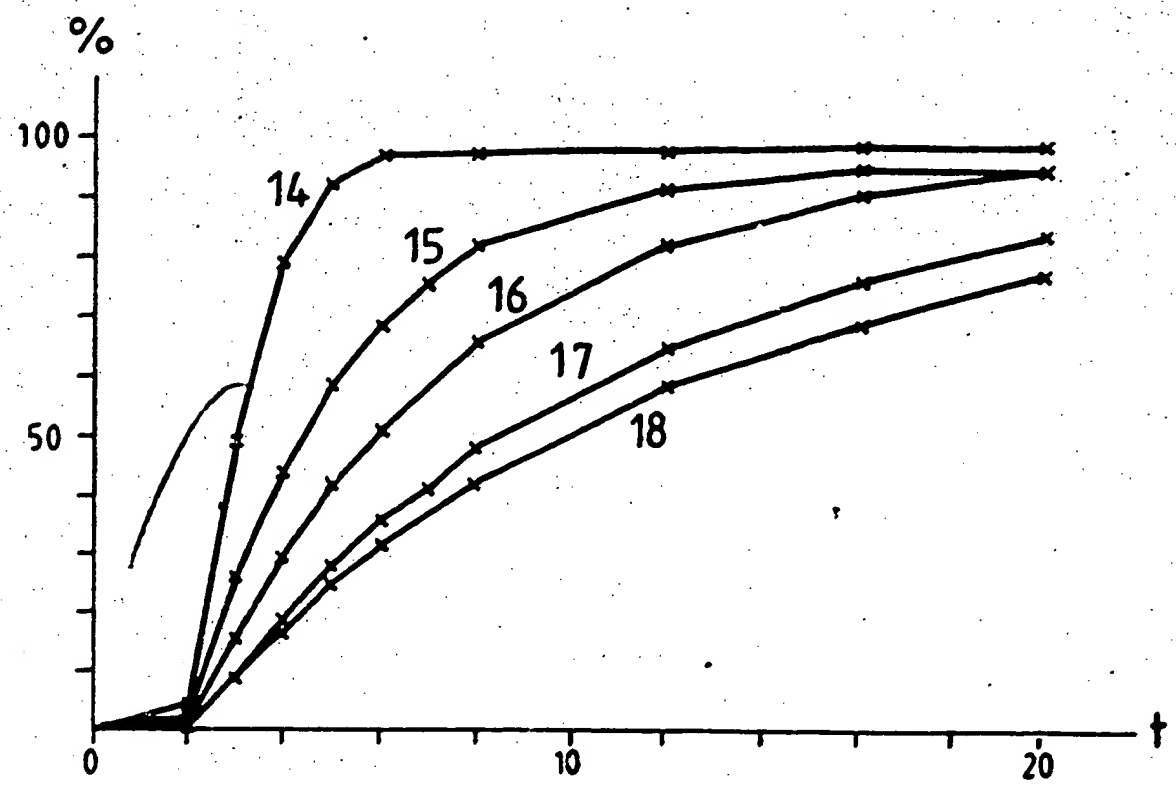

FIG. 5

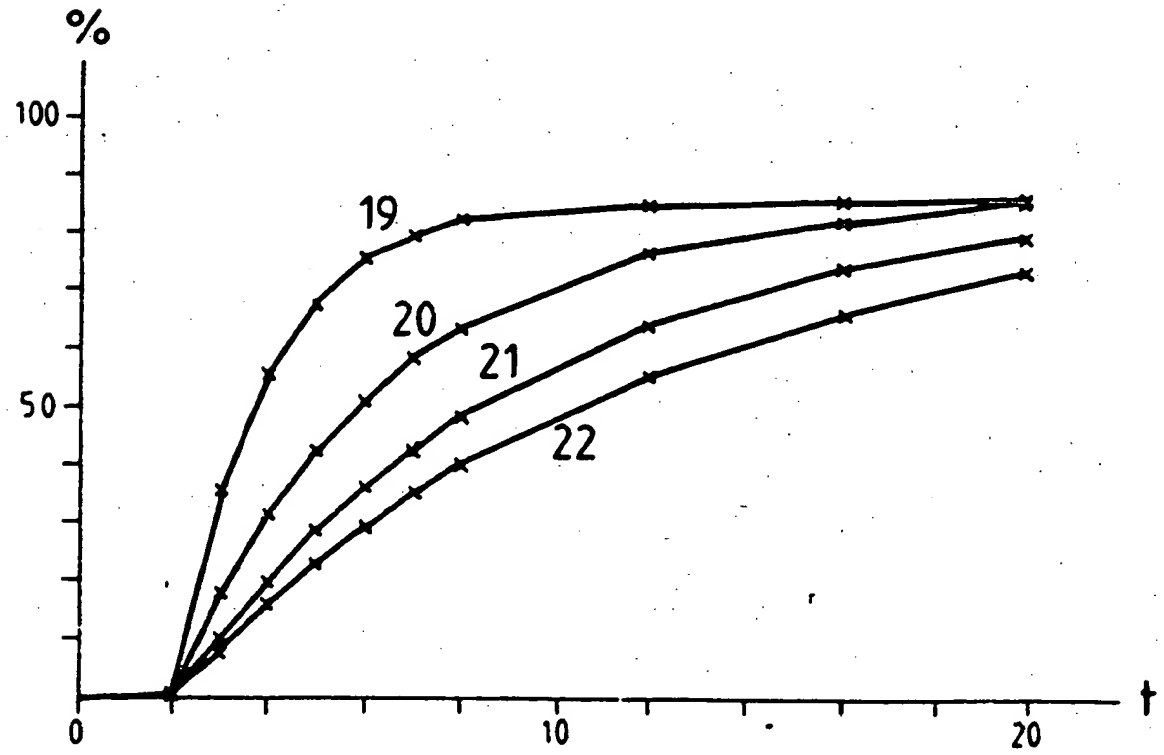

FIG. 6

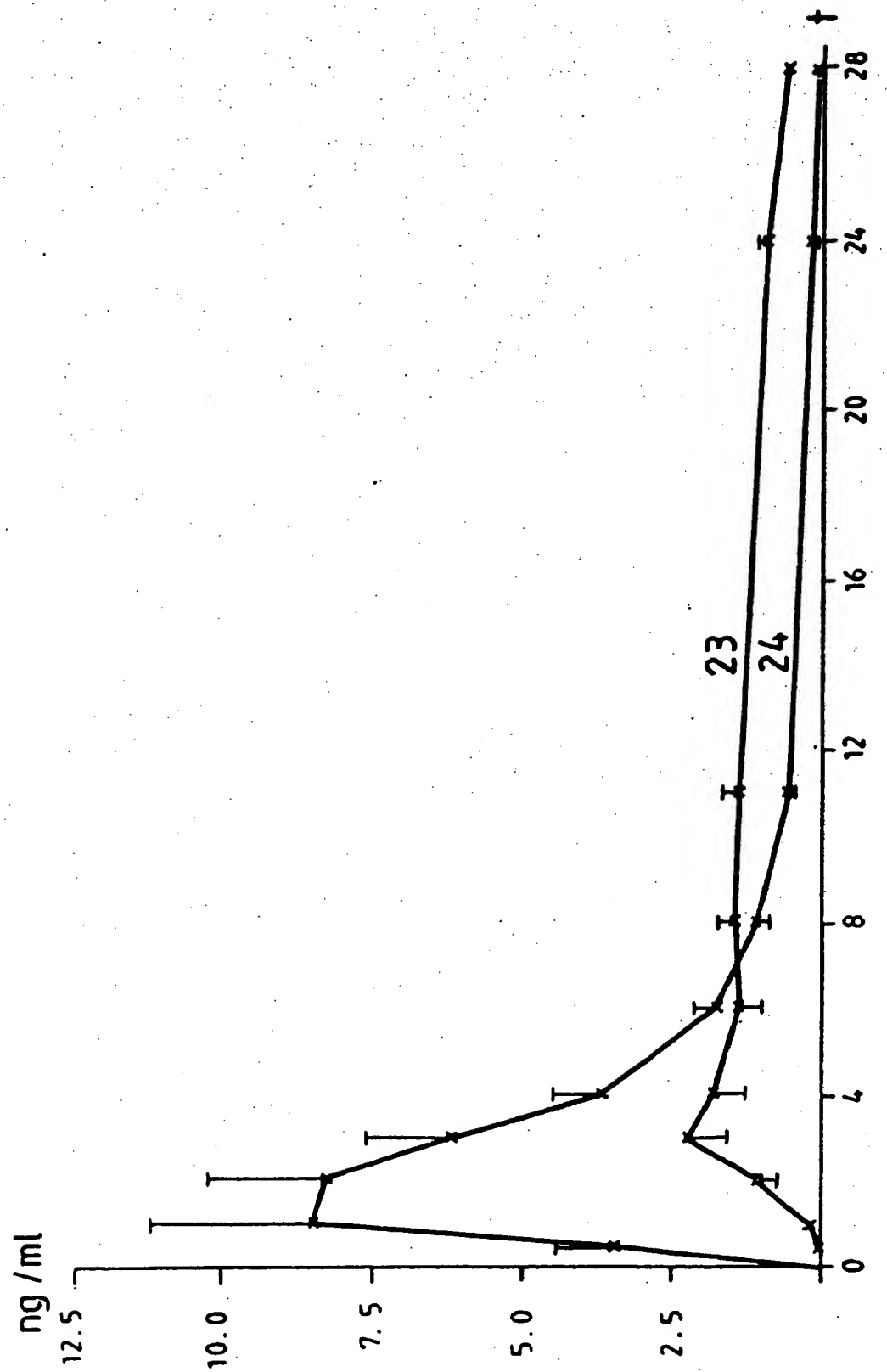

FIG. 7

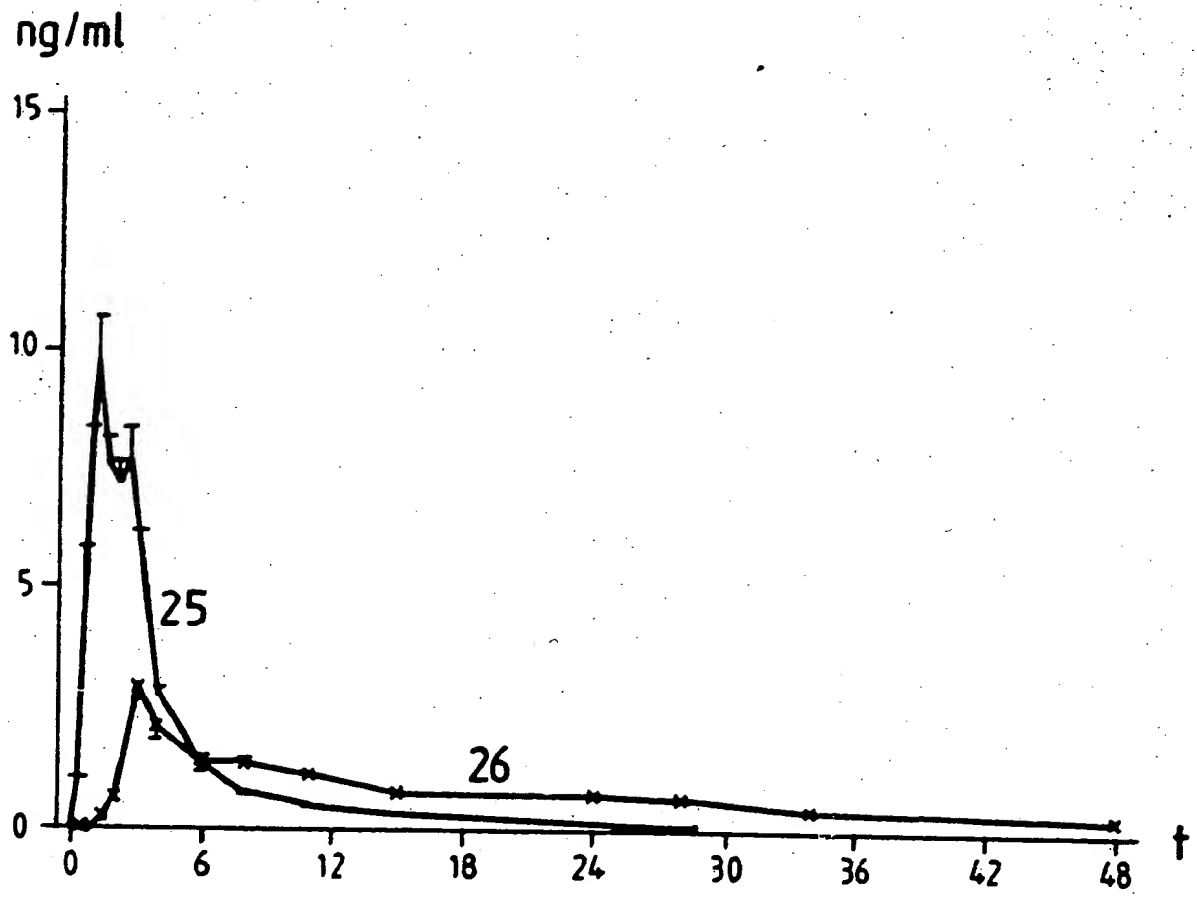

FIG. 8

SPECIFICATION

N vel galenical retard f rm

The invention relates to forms of pharmacologically active agents having contr lled release properties and especially to solid dispersion forms of such agents having sustained release properties of the agent in an aqueous medium.

By incorporating an active agent in a solid dispersion or solution up till now merely an accelerated release was realized: For example solid dispersion forms of medicaments are known, e.g. from the German Offenlegungsschrift No. 2.549.740, in which solid dispersions of griseofulvin in polyethylene glycol are described. The low dissolution rate and accordingly (see page 11, lines 4-5) the low bioavailability of griseofulvin were improved by the preparation of a solid dispersion of griseofulvin in polyethylene glycol. In the specifically described medicament formulation, a tablet, a disintegrant had to be added to the solid dispersion granulate since it appeared that a greatly improved dissolution rate of griseofulvin was again receded. The pressure applied in the production of tablets led to considerable cohesion between the tablet particles as a result of the strong cohesion between the polyethylene glycol molecules.

The disintegrant, crosslinked polyvinylpyrrolidone was added, in order to be able to re-form the original granulate particles of the tablet, in which the griseofulvin was present in a faster soluble form.

The water soluble polyethylene glycol, in contact with an aqueous medium, is extracted from the granulate by diffusion, the finely divided griseofulvin coming into a situation to dissolve quickly.

According to the German Auslegeschrift No. 2.546.577 an increase of the dissolution rate and the resorption of salts of difficulty water soluble ergotamine compounds (especially of dihydroergotamine-methanesulfphonate, of dihydroergocristine-methanesulphonate, of dihydroergocryptine-methanesulphonate and of dihydroergocornine-methanesulphonate) is obtained when the salts are present in solid solutions in polyalkylene glycols and especially in polyvinylpyrrolidone of a molecular weight above 10.000. The mentioned drugs have in methanesulphonate salt form a water solubility above 0.01 % and are in this respect distinguished from the active agents used according to the invention.

According to the European application No. 78430 an increase of the dissolution rate and a maintenance of the resorption of dihydropyridines, especially of Nifedipine and of Nimodipine is obtained on dissolving th s agents together with polyvinylpyrrolidone, e.g. having a molecular weight of 25.000, in a small quantity of a liquid organic solvent such, that the solid particles are only just dissolved after which this solution is mixed and granulated with solid carriers having a large capacity to absorbe, leading to evaporation of the organic solvent.

Th drug is present in the solid polyvinylpyrrolidone in a dissolved state and shows on contact with an aqueous medium an increased dissolution rate. Both these features distinguish these known products from th compositions of the present invention.

According to the Canadian patent No. 987.588 an increase of the dissolution rate and of the bioavailability of difficulty water-soluble drugs is obtained when they are present as solid dispersions in polyethylene glyc ls and in other water-soluble matrix materials, e.g. pentaerythritol, pentaerythritol tetraacetate or citric acid.

Th known drugs digitoxin 17-methyltestosterone, prednisolone acetate and hydrocortisone acetate are present at concentrations up to 5 % in the matrix material, thus giving dispersions which are different from the dispersions according to the present invention. The drug griseofulvin has, as indicated above, a water-solubility of more than 0.01 % and is therefore distinguished from the active agents used according to the inver.tion.

We have discovered that if solid dispersions of pharmacologically active agents, practically insoluble in water ar employed in such a matrix material, no significant expected increase of the dissolution rate in aque us medium is observed. Instead a decrease is obtained, without a material loss of bioavailability.

We have additionally discovered, that the decrease of the dissolution rate may be attributed to a coherent crystalline form of the drug, hereinafter referred to as a secondary structure, which form may be maintained even if the water-soluble matrix material is removed on contact with an aqueous medium, e.g. water.

T permit the secondary structure to be formed, it is preferred to have the drug in the solid dispersion present in a concentration above 5%, and for more than 5 percent by weight in a crystalline form preferably as particles of a diameter below 5 micrometer and having a water-solubility up to 0.01 %, preferably below 0.005 percent by weight.

The present inv ntion therefore pr vides in one aspect a solid disp rsion f a pharmacologically active agent in a water-soluble crystalline matrix as a carrier, in which th active agent

a) has a maximum solubility of 0.01 % at 37 C in water,

b) is present in the matrix at a total concentration of above 5 percent by weight, and

c) is present in the matrix at a concentration of above 5 percent by weight in a coherent crystalline form.

This solid dispersion has in an aqueous medium a decreased dissolution rate.

A decreased dissolution rate was established in the following cases in the art:-

German Offenlegungsschrift No. 1.617.362 describes suspending pharmacologically active agents, particularly theophylline, in molten waxes for the preparation of galenical forms having a decreased dissolution rate in a aqueous medium. As a wax polyethylene glycol is used.

However, the solubility of theophylline is not low enough (above 0.01 %) and nly the additional incorporation of conventional retardation excipients, lik beeswax or stearic acid can cause a satisfactory decrease of the dissolution rate of the drug.

According to German Offenlegungsschrift No. 3.318.649 a two phasic solid pharmaceutical composition is described which contains crystalline Nifedipine and separately a solid solution of Nifedipine in a matrix material, particularly in polyvinylpyrrolidone. On contact with an aqueous medium, Nifedipine is dissolved from the solid solution at an increased dissolution rate and from the solid Nifedipine crystals at a decreased dissolution rate.

According to the present invention only a solid dispersion of the drug is present, which on contact with an aqueous medium causes the release of the drug at a decreased rate.

For the solid dispersion according to the invention the choice of the pharmacologically active agent is not critical, provided that its solubility and crystallisation conditions are met.

It is a simple and routine matter to test whether a given active agent complies with the required conditions.

Th practically insoluble pharmacologically active agents in the dispersion according to the invention are e.g. dihydropyridines, particularly the 1,4-dihydro- 3,5-dicarboxylic acid diester-2,6-dimethylpyridines, especially such having an optionally substituted 4-phenyl or a 4-phenyl derivative group.

A 4-phenyl derivative group is e.g. the 4-(2,1,3- benzoxadiazol-4-yl) group. An example of a drug having an optionally substituted 4-phenyl residue is the known 4-(2-nitrophenyl)-1,4-dihydro-2,6-dimethyl-5-methoxycarbonyl-3-pyridine carboxylic acid methylester (nifedipine).

Examples of drugs having a 4-phenyl derivative group are 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-ethoxycarbonyl- 2,6-dimethyl-3-pyridine carboxylic acid ethyl ester (compound A), 4-(2,1,3)-benzoxadiazol-4-yl)-1,4- dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester (compound B) and (-)- (S)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5- methoxycarbonyl-1,2,6-trimethyl-3-pyridine carboxylic acid isopropylester (compound C).

The dihydropyridines are extensively described in the Literature and have particularly a calciumantagonistic activity. They are described e.g. as antihypertonics and as medicaments to treat angina pectoris.

The above-mentioned dihydropyridines A and B are known, e.g. from the European patent No. 150 and the British patent No. 2.037.766. The dihydropyridine C is known from the British patent application GB 2.122.192 A, and is specifically described in Example 2c thereof.

It has been established, that the dihydropyridines, e.g. the compounds A and B are practically water-insoluble and thus have a water solubility of less than 0.01 %.

Processing of them into a solid dispersion form however did not, as expected, result in an increased dissolution rate but surprisingly in a significantly decreased dissolution rate (see the comparative tests 1 to 5), advantageous in compositions which are to be administered once a day.

This retard effect is attributed to the solid dispersion, e.g. in granulate form, independent of optionally present excipients. An advantage is that no customary drug burst appears and that there is not significant decrease of the bioavailability (see the comparative tests).

The present invention thus provides a pharmaceutical composition for administration once a day, containing a therapeutical effective amount of the compounds A or B. The matrix materials are preferably pharmaceutical acceptable solid compounds conventionally widely used as pharmaceutical excipients. Since they must preferably be water-soluble, they should have polar properties. Most of these matrix materials thus have polar groups, e.g. oxy groups, especially hydroxy groups.

The preferred pharmaceutical compositions contain a solid dispersion of pharmacologically active agents in a polyalkylene glycol, particularly in a poly(C$_{2-3}$)alkylene glycol, e.g. in a polyethylene glycol. The polyethylene glycol preferably has a molecular weight from 1000 to 20.000, especially from 4.000 to 20.000, particularly from 4.000 to 8.000, e.g. 6.000.

The solid dispersions may be obtained by dissolving the active agents at a concentration above 5 percent by weight, in the liquified dispersing agent and solidifying the obtained mixture.

Liquifying the dispersing agent may occur by melting or by addition of a liquid organic solvent.

Solidifying of the liquid active agent containing dispersing agent may occur e.g. by cooling or by evaporating the liquid organic solvent.

The present invention thus also provides a process for the preparation of a solid dispersion of a pharmacologically active agent in a crystalline matrix as a carrier, characterized in that an active agent, having a maximum solubility of 0.01 %, preferably below 0.005 %, in water at 37 C, is dissolved at a concentration of above 5 percent by weight in a liquified matrix and the obtained mixture is transformed to a solid form and the active agent is crystallized.

After obtaining the solid dispersion it may be reduced to a conventional particle size, giving a granulate useful for further processing.

At least 5 percent of weight of the drug particles present in the solid dispersion are so small, that it is impossible to see them by conventional optical measurements, since if suspended for measurement purposes in an aqueous medium, they appear to have a Brownian perpetual motion.

Hence the particles are assumed generally to have a diameter f 5 micrometres or less.

Laserlight scattering tests in the aqueous suspension established a particle size of even less than 0.5 micrometer.

Comparison f the Guinier-de W lff-spectra of the s lid dispersion and f a corresponding mechanical mixture showed no significant difference.

The sp ctra show further that both drug and matrix material in the dispersion are in a crystalline form.

The concentration of the drug in the matrix may vary from 5 to 80 %, especially from 20 to 50 %, and particularly from 20 to 40 percent of weight and contributes to the sustained release effect according to the invention. (Greater concentration may cause a greater decrease of the dissolution rate, see curves 14 to 18 in Fig. 5 for the dissolved quantity in percent of weight versus time T in hours; increasing concentrations of 10 to 50 percent by weight of compound A may cause a decrease of the dissolution rate).

Curves 14 to 18 in Fig. 5 relate to solid dispersion granulates of the same subfraction, containing 10, 20, 30, 40 and 50 percent by weight of compound A.

The appropriate dose of the active agent amounts preferably up to 250 mg and preferably up to 200, especially up to 100 mg for compound A and up to 50, preferably up to 30, especially 10 to 25 mg for compound B per day. For a rationally administrable dispersion quantity a concentration from 10 to 80% of active agent in the matrix, on the average up to 50%, e.g. 40% of compound A and 20 percent by weight of compound B are indicated.

If the ch mical stability of the active agent is not high, then the temperature of the molten matrix material, e.g. of the polyalkylene glycol, should be kept appropriately low. If more active agent is added to the polyalkylene glycol, then can be dissolved at the maximum allowable temperature; the excess will not be dissolved, but will be incorporated as a suspension.

The undissolved fraction particles preferably should have a particle size of at most 100 micrometres.

After cooling of the suspension these particles may be found in the dispersion with an similar size in addition to the fraction of active agent, that was dissolved and after cooling can be found again in the form of crystals having a diameter of at most 5 micrometres.

In the granulating process, briefly described above, the solid dispersion is preferably reduced to a particle size from 50 to 2000 micrometer, especially from 90 to 1000, mor particularly from 125 to 500 micrometer.

The particle size of the granulate contributes to the controlled release effect according to the invention (larg r particles cause a greater decrease of the dissolution rate, see curves 9 to 22 in Fig. 6; dissolved quantity in percent by weight versus time T; an increasing particle size causes a decrease of the dissolution rate, curves 19 to 22 relate to sieve factors of 90 to 180, of 180 to 355, of 355 to 500 and of 500 to 710 micrometre respectively of the dispersion granulate of a 40% dispersion of compound A in polyethylene glyc l 6000.

Summarizing, it may be concluded that the release of the pharmacologically active agent can be controlled by changing the concentration of the active agent in the solid dispersion as well as by varying the particl size of the solid dispersion granulate.

Surprisingly, it has been established that when the dispersion granulate particles, e.g. those of Example 1, ar brought into water, their matrix fraction is dissolved quickly and quantitatively. The active ag nt particles which in the dispersion have for example a size of up to 5 micrometre, form coherent s condary structures, their density and diameter varying according to the concentration of the active agent in the matrix and the diameter of the granulate particles.

The pres nt invention thus provides a secondary active agent structure, formed from the solid dispersion after selective extraction of the matrix material, e.g. in an aqueous medium. This secondary structure may have a diameter comparable to that of the dispersion granulate. It shows in water a retarded dissolution rate. It can be partially restored to its original particles of up to 5 micrometre by intensive ultras nic treatment.

Particles of active agent which in the dispersion granulate may have for example a diameter of up to 100 micrometre are in the secondary structure, which has been proceeded from the particles of up to 5 micrometre, enclosed in an unchanged state.

Since the original agent particles up to 5 micrometre and the additionally enclosed agent particles up to 100 micrometre contribute to the controlled release effect, both their solid dispersions and secondary active agent structures belong to the present invention.

The diam ter and the surface of the secondary structure particles of the active agent have been investigated. They show irregular fissurelike channels and have an external and an internal surface.

Both the size and the structure of the external surface influence the dissolution rate in an e.g. aqueous, solvent medium. The internal surface shows narrow pores up to 1 micrometre which hardly contribute to the release of active agent,since if they c ntain a solvent medium, its mobility is strongly reduced.

The size of the secondary structure corresponds to the size of the solid dispersion granulate particles, from which they originate.

After removal of the solvent medium, e.g. by drying, the specific surface and the pore volume are measurable.

The present invention provides the secondary structure of an active agent of a diameter of preferably from 50 to 2000, more particularly from 90 to 1000, especially from 125 to 500 micr metre, having a porous structure, characterized by a specific surface of 1 to 15 m^2/g, pref rably from 2 t 12 −2/g, measured according to the BET-method and by a pore volume of 20 t 95%, measured by mercury-por sime-try.

The solid dispersion particles as well as the secondary structure particles are usable for the preparation of pharmaceutical compounds.

The present invention thus provides also pharmaceutical compositions containing the solid dispersion granulate or the secondary structure particles.

Pharmaceutical compositions containing the solid dispersion granulate can be considered as galenical precursor forms of corresponding compositions containing the secondary structure particles, since their behaviour in the body is comparable with that of pro-drugs.

For the preparation of the pharmaceutical oral administration forms containing the solid dispersion, the granulate of the solid dispersion may be mixed in a conventional manner with suitable pharmaceutical excipients, e.g. a filling agent, such as lactose, a glidart, e.g. silicon dioxide and a lubricant, e.g. magnesium stearate (see. e.g. examples 2, 5, 6 and 9) and optionally a desintegrant, such as crosslinked polyvinylpyrrolidone, e.g. crosspovidone (see e.g. examples 2, 3, 5 and 6), or sodium carboxymethylcellulose (see example 9) and may be manufactured to conventional solid oral administration forms, such as tabl ts or capsules.

For the preparation of tablets the solid dispersion granulate may preferably be mixed with e.g. lactose, silicon, dioxide and magnesium stearate (see example 4, 5, 6 and 9).

The porous secondary structure agent particles are preferably used in capsules, since they are less able to r sist the pressure for tabletting.

For the preparation of capsules, the solid dispersion granulate of the secondary structure agent particles may be mixed in conventional manner preferably with a placebo granulate from suitable excipients like lactose, starch and polyvinylpyrrolidone and with a mixture of crospovidone, silicone dioxide and magnesium stearate (see examples 2 and 3). The desintegrant may be used for suspending the capsule content.

Generally pharmaceutical administration forms, especially capsules and to a lower extent tablets as well show, during the passage through the stomach, a drug burst, which can to a large extent be prevented by applying an enteric coating on it. Suitable enteric coatings include hydr xypropylmethylcellulosephthalate (see example 3,5,6 and 12). If the active agent is resorbed in the upper part of the intestines - dihydropyridines are such agents - then such a coating is very beneficial and does not impair the resorption process.

Tablets, which contain the components in compressed state, may need this coating to a lower extent, but then the desintegrant should be omitted (see the tablet of example 4, which contains no crosslinked polyvinylpyrrolidone).

We have established, that capsules or tablets without an enteric coating may be made if a hydrophobic excipient, such as a fatty acid glyceryl ester, is added to the solid dispersion (see examples 8 and 9 and comparative test No. 4). This hydrophobic ester reduces the drug burst in the stomach and may not significantly disturb the resorption process in the intestines. Such compositions may be prepared by dissolving the pharmacologically active agent in the liquid matrix and emulgating the obtained mixture with the hydrophobic substance, e.g. the fatty acid glyceryl ester, as much as possible, after which the obtained mixture may be solidifed by cooling.

Preferred fatty acid glyceryl esters are physiologically acceptable esters, like (C_{10-20})fatty acid, e.g. palmitic and or stearid acid glyceryl esters. These esters may be, e.g. mono-, di- and or triesters of glycerin.

The amount of fat is preferably up to 60 percent of the total weight of the solid dispersion, e.g. 5 to 60°o, and is partiuclarly up to 15 to 25°o, e.g. 20°o.

The sustained release compositions according to the invention may be used to administer very different, practically water insoluble classes of active agents. They may be used for their known indications.

The quantities of active agents to be administered may be dependent on various factors, e.g. the conditions to be treated, the duration of treatment desired and the rate of release of the active agents.

The amount of each active agent required and the rate of release may be determined using in vivo techniques, e.g. measuring the concentration of active agent in the blood serum.

The pharmaceutical compositions of e.g. the compounds A and B may be used e.g. for the same indications as described in the European patent No. 150 and in the British patent No. 2037766.

For the antihypertonic use e.g. up to 250, especially up to 200, particularly 50 to 100 mg of compound A and up to 50, especially up to 25, particularly 10 to 20 mg of compound B are used per day.

The present invention provides especially a pharmaceutical composition for plasma levels of 2 to 8 ng of compound A per ml during at least 22 hours, in the event that it contains one dosis of 50 mg of the active agent. Basis for this observation are the plasma level curves 1, 3, 4, 5 and 6 to 13 in Fig. 1 to 4.

The present invention also provides a pharmaceutical c mposition for plasma levels of 1 to 2,5 ng of compound B) per ml, during at least 22 hours, in the event that it contains one dosis of 10 mg of th active agent. Basis for this observation are the plasma level curves 23 and 26 in Fig. 7 and 8.

The plasma level of compound A for curves 1 to 13 in Fig. 1 to 4 (c ncentrations vs. time) may be determined gaschr matographically.

A plasma sample of 1 ml, adjusted with NaOH to pH 13, was extracted with toluene, the toluene was evaporated and the residue diss lved in 0.5 ml of toluene. 2 microlitres of the formed solution were separated at 300°C in a OV 17 column (6% on Gaschrom Q 100- 120 mesh) using a argon/methane gas (95.5 volume/volume) mixture as a carrier gas (rate 60 ml/min). The analysis may be carried out using an electron capture detector. The retention time of compound A was 3.1 min.

The concentration of the compound was calculated by peak measurement in comparison to the peak of an internal standard. The detection limit is 0.5 ng of active agent per ml of plasma.

The dissolution rate of compound A in vitro for curves 14 to 22, of compound C in example 13 and of nifedipine in example 14 (dissolved quantities in percent by weight vs. time) was determined in 1000 ml of solvent medium at 37°C according to the Rotation-Paddle- Method (USP XX) at 50 rotations per min. For compound A and for nifedipine an aqueous 0.1 HCl solution was used as the solvent medium. After 2 hours the pH was adjusted by addition of a tenside containing buffer solution of pH 6.8. Compound C was tested in a netural tenside containing aqueous solution.

20 microlitres of a filtered sample of the solution of active agent and of a reference solution were separated chromatographically in 2 columns of a length of 10 cm and a diameter of 4.6 mm, containing substance RP.18; 5 micrometre as a stationary phase and with methanol/water 85:15 (v/v) as a mobile phase and at a pressure of 150 bar at room temperature and were measured at a wave length of 326 mm.

The plasma levels of compound B for curves 23 to 26 in Fig. 7 and 8 were chromatographically determined as well. A plasma sample of 2 ml, adjusted with NaOH to a pH 13, was extracted with toluene. The toluen was evaporated and the residue dissolved in 25 microlitre of toluene. 2 microlitre of the formed solution were separated at a temperature of 300°C in a OV 17 capillary column (internal diameter of 0.3 mm and a length of 25 m), using helium as a carrier gas, (pressure at the input: 0.7 atm. of excess pressure).

Th analysis was carried out at a temperature of 300°C using an electron capture detector with an argon methane (90:10 vol vol) gas mixture (rate 30 ml/min) as additional gas. The retension time of compound B) was 11.5 min.

The calculation of the concentration of compound B was carried out analogously as described for compound A. The detection limit is 50 picogram of active agent per ml of plasma.

Example 1: 4-(2,1,3-benzoxadiazol-4-yl)-1,4- dihydro-5-carboxy-carbonyl-2,6-dimethyl-3-pyridincarboxylic acid ethylester (compound A)

Preparation of the solid dispersion:

4 parts by weight of scaly polyethylene glycol 6000 are melted at 55 to 63°C and heated to about 85°C while stirring.

One part by weight of compound A are added and dissolved completely while stirring at a constant temperature. The solution is then rapidly cooled by pouring it into a metal sheet, where it solidifies in a layer thickness of about 2 mm. After cooling to room temperature the solidified layer is detached from the sheet, reduced to coarse pieces and then passed in stages through sieves of decreasing mesh (2.5, 1.0 and 0.5 mm) or reduced to small pieces in a hammer-mill so that a granulate is produced, usable for the preparation of a tabletting or capsulating mixture.

Example 2

Hart gelatine capsule

Components			quantities in mg
1.	Compound A - polyethylene glycol 6000 granulate (20%), prepared according to example 1		250.0
2.	Placebo granulate of		
	Lactose	83 parts	
	Cornstarch	10 parts	
	Polyvinylpyrrolidon	6 parts	41.0
3.	Crosslinked polyvinylpyrrolidone		6.0
4.	Silicon dioxide		1.5
5.	Magnesium stearate		1.5
			300.00

Both granulates 1.and 2.are mixed. Components 3. to 5. are mixed as well, after which the mixture of 1. and 2. is mixed with the mixture of 3. to 5. and is filled in gelatine capsules of a suitable capacity.

Example 3

The hard gelatine capsule f example 2 is enteric coated in conventional manner in Wurster column with a mixtur f

	hydroxypropyl-methylcellulose-phthalate	33.3 mg
	and	
	diethylphthalate	3.3 mg

Example 4:

Tablet

Components		quantity in mg
1.	Compound A - polyethylene glycol 6000 granulate (20%), prepared according to example 1	250.0
2.	Lactose, anhydrous	188.5
3.	Silicon dioxide	2.5
4.	Magnesium stearate	9.0
		450.0

The components 1. to 4. are briefly mixed, the mixture is sieved (630 mikrometre mesh), mixed again and tabletted in conventional manner.

Example 5

Tablet

Components:		quantities in mg
1.	Compound A - polyethylene glycol 6000 - granulate (20%), prepared according to example 1	250.00
2.	Lactose, anhydrous	177.25
3.	Crosslinked polyvinylpyrrolidone	11.25
4.	Silicon dioxide	2.50
5.	Magnesium stearate	9.00

Th components 1. to 5. are mixed and tabletted as described in example 4.
The tablet is enteric coated as described in example 3 with a mixture of

	hydroxypropyl-methylcellulose-phthalate 9%	
	and	
	diethylphthalate 9%	50.0
		500.00

Example 6:

In an analogous manner as described in example 1, a 4% dispersion of compound A in polyethylene glycol 6000 is prepared at a temperature f 125°C The dispersion granulate is, in a manner as described in example 5, compressed to tablets containing 50 and 100 mg of active agent.

Tablets

Components:		quantities in mg	
1.	Compound A - polyethylene glycol 6000 granulate (40%)	125.0	250.0
2.	Lactose, anhydrous	65.0	130.0
3.	Cross-linked polyvinylpyrrolidone	5.0	10.0
4.	Silicon dioxide	1.0	2.0
5.	Magnesium stearate	4.0	8.0
	enteric coating*	20.0	40.0
		220.0	440.0

*A coating of	percents by weight
hydroxypropylmethylcellulosephthalate	93
Titanium dioxide	3.5
Iron oxide, yellow	3.5

The coating is applied to in conventional manner in a Wurster column

Comparative test No. 1

A conventional uncoated hard gelatine capsule containing a granulate of components 1. to 5. and an xternal phase of a mixture of components 6. to 9.

		quantities in mg
1.	Compound A	50.0
2.	Lactose	216.0
3.	Cross-linked polyvinylpyrrolidone	6.0
4.	Polyoxyethylene-polyoxypropylene polymer	10.0
5.	Polyvinylpyrrolidone	7.5
6.	Cross-linked polyvinylpyrrolidone	5.5
7.	Polyethylene glycol 6000 (solubilizing agent)	10.0
8.	Corn starch	52.0
9.	Magnesium stearate	3.0
		360.0

was compared with the enteric coated retarded capsule of example 3 and with the uncoated retarded capsule of example 2.

In 8 healthy fasted male volunteers of 19 to 40 years the enteric coated retarded capsules of example 3 produced almost constant plasma levels of compound A (above 5 nanogram ml) from 3 hours till 28 hours after administration (mean curve 1 in Fig. 1).

Conventional hard gelatin capsules caused in the same volunteers the conventional picture of mean curv 2 in Fig. 1, the active agent for the most part being released within 6 hours. The areas under both curv s 1 and 2 are almost the same: AUC_{∞} * = 210 and 196.2 nanograms ml h respectively. This indicates that the capsule of the invention has no significant loss of bioavailability.

In a second test the uncoated retarded capsule of example 2 was administered to 8 healthy male volunteers. 4 of the volunteers were also participants in the first test with the enteric coated retarded capsule. In comparison to the conventional capsule (curve 2) a retard effect is obtained (mean curve 3, in Fig. 1). However, the uncoated retarded capsule of example 2 has a tendency to cause a drug burst (curve 3).

From both tests it can now be established, that the combination of the new solid dispersion granulate with the enteric coating has an excellent contr lled release effect.

The retarded capsules of examples 2 and 3, particularly the enteric coated of example 3, make a once-a-day-administration possible; of the conventional form 2 to 3 capsules have to be taken a day in regular periods of time.

* UAC = Area under the curve (extrapolated to infinite)

Comparative test No. 2

The conventional uncoated hard gelatine capsule of comparative test No. 1 was c mpared again, but instead with the enteric coated retarded tablet of example 5, and tested in another group of 8 healthy male volunteers.

The enteric coated retarded tablet of xample 5 produced plasma lev ls of the mean curve 4 in Fig. 2 and the conventional capsule of comparative test No. 1 produced a mean result, comparable with curve 2. The enteric coated retarded tablet of example 5 produced practically constant plasma levels of compound A (about 6 to 7 ng ml), from 5 and till 32 hours after administration (curve 4).

Again, there is no significant loss in (relative) bioavailability, using the enteric coated retarded tablet. It makes a once-a-day-administration possible. The conventional hard gelatine capsule has to be taken 2 to 3 times a day.

Comparative test No. 3

In a further human study with 8 healthy male subjects, the normal uncoated capsule, described in comparative test No. 1, was compared in a cross-over design with three additional formulations, including the enteric coated retarded tablet of example 6 containing 50 mg of compound A in a 40% solid dispersion in polyethylene glycol 6000.

In this study all formulations were administered to the fasted subjects with 150 ml of water. A standard breakfast was given 2,5 h later.

The mean curve 5 in Fig. 3 shows the plasma levels of the enteric coated retarded tablet up to 72 hours.

Concentrations between 3 and 5 ng ml are obtained from 7 to 36 hours after digestion, a duration of absorption lasting 29 hours. In comparison to the normal capsule the relative bioavailability of the retard tablet was 88%, with a standard deviation of 36%. This value is not statistically different from 100%, on the basis of a paired t-test, indicating no loss of bioavailability.

A remarkable feature of the pharmacokinetic behaviour of this retard tablet is the relatively low intra individual variability, seen in the individual kinetic profiles curves 6 to 13 in Fig. 4.

In all cases the plasma levels are seen to fall within the 2 to 8 ng/ml range with no significant drug burst occuring in any subject. Furthermore, the presence of the gastro-ristant coating gave a highly reproduceable lag time prior to absorption (2.6 ± 0.8 h) when the tablets were administered in the fasting stat .

These results demonstrate, that an enteric coated tablet composed of a 40% solid dispersion perform an excellent form to permit a once-a-day application of 50 mg and potentially higher doses, e.g. 100 mg of drug.

Example 7: 4-(2,1,3-benzoxadiazol-4-yl)-1,4- dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic acid isopropylester (compound B)

Preparation of the solid dispersion and of the dispersion granulate:

6 parts by weight of polyethylene glycol 6000 are mixed with 2 parts by weight of a commercial mixture comprising mono-, di- and triesters of palmitic and stearic acid and glycerol (Prectrole®) and with 2 parts by weight of compound B, then melted at a temperature of 75 to 85,dgC and dissolved as much as possible while intensive stirring at a constant temperature of 70 C. The mixture is then cooled rapidly to room temperature by pouring it onto a precooled metal sheet and keep at 4 C for 3 hours. It solidifies as a layer of approximately 4mm thickness.

The solidified layer is reduced to coarse particles, which are passed through a hammer mill (type Fitzpatrick, USA) thus producing a granulate usable for the preparation of a tabletting or capsulating mixture.

The characteristic grain size of the RRS-B-distribution - X' ca 320 micrometre.
n ca. 3 (reciprocal measure for the distribution range)
(H. Sucker, c.s. Pharmazeutische Technologie, Georg Thieme Verlag, Stuttgart 1978, page 110).

Example 8

Tablet

	Components:		quantities in mg:
1.		Compound B - polyethylene glycol 6000 - fatty acid glyceryl ester mixture-granulate (produced according to example 7)	50.0
2		Lactose, anhydrous	68.8
3.		Magnesium stearate	1.2
			120.0

*Trademark of Gattefosse

The components 1. and 2. are briefly mixed (5 min.). The mixture is sieved (mesh: 800 micrometres), sieved again (10 min.), mixed with component 3. (5 min.) and tabletted in conventional manner on a rotary tabletting machine.

The tablets have a diameter of 7 min. and show a compression strength of 46 Newton.

Example 9.

Tablet

	Components:		quantities in mg.
1.		Compound B - polyethylene glycol 6000-fatty acid glyceryl ester mixture granulate (according to example 7)	50.00
2.		Lactose, anhydrous	61.42
3.		Silicon dioxide	0.23
4.		Sodium carboxymethycellulose	2.20
5.		Magnesium stearate	1.15
			115.00

The components 1. 2. and 4. are briefly mixed (5 min.), the mixture sieved (mesh: 800 micrometres) and mixed again(10 min.).

The components 3. and 5. are mixed together with a part of the mixture 1., 2. and 4., sieved (800 micrometres) and mixed with the remainder of the mixture of 1., 2. and 4. (5 min.).

Comparative test No. 4

A conventional uncoated hard gelatine capsule containing a mixture of components 1 to 6

		quantities in mg
1.	Compound B.	10.0
2.	Lactose (filler)	167.0
3.	Sodium laurylsulphate (solubilizing agent)	5.5
4.	Silicon dioxide (glidant)	1.5
5.	Corn starch (desintegrant)	128.0
6.	Polyethylene glycol 6000 (solubilizing agent)	8.0
		320.0

was compared with the retarded tablet of example 8. In 8 fasted healthy male volunteers in an age of 19 to 40 years, the retarded tablet of exampl 8 showed practically constant plasma levels of drug between 2.3 and 1 ng ml and, on an average, between 1.5 and 1 ng ml from 2 to 24 hours after administration (see mean curve 23 in Fig. 7). The non-retarded conventional capsule showed in the same volunteers the conventional picture of mean curve 24 and a drug rel ase within 6 hours.

The areas under both curves 23 and 24 are practically the same: By comparison of the AUC of curves 23 and 24 a relatively bioavailability of ven 96.2% for the retard tablet of exampl 8 could be established.

The retard tablet of example 8 produced, compared with the conventional uncoated hard gelatine capsule, a hardly detectable drug burst.

Whereas 2 to 3 conventional capsules must be administered a day, divided over regular peri ds of time, the retarded tablet makes a once-a-day administration possible.

Example 10:

Preparation of the solid dispersion and f the dispersion granulate:

10 parts by weight of compound B are dissolved at a temperature of 125°C in liquified polyethylene glycol 6000.

The mixture is quickly cooled to room temperature by pouring it onto a precooled metal sheet and is kept over night.

The solidified layer is reduced to coarse particles and passed through a hammer mill (typ Fitzpatrick, USA) to obtain a granulate, usable for the preparation of a tabletting or capsulating mixture.

Example 11:

Tablet

Components:		quantities in mg
1.	Compound B - polyethylen glycol 6000 - granulate (20%, prepared according to example 10)	50.00
2.	Lactose, anhydrous	63.85
3.	Magnesium stearate	1.15
		115.00

The tablet is produced in an analogous manner as described in example 8 (the sieve had a mesh of 1250 micrometre).

Tablets: diameter 7mm
compression strength: 40 Newton

Example 12:

The tablet of example 11 is enteric coated in a conventional manner in a Wurster column with a mixture of

	quantities in mg
hydroxypropyl-methylcellulose-phthalate	13.8
Iron oxide pigment, red.	0.6
Titanium oxide	0.6
	15.0

Comparative test No. 5

Two conventional not retarded capsules each containing a mixture of components 1 to 6

		quantities in mg
1.	Compound B	5.0
2.	Lactose	172.0
3.	Sodium laurylsulphate	5.5
4.	Silicon dioxide	1.5
5.	Corn starch	128.0
6.	Polyethyleneglycol 6000 (solubilizing agent)	8.0
		320.0

were compared with the enteric coated retard tablet of example 12.

The test was carried out as described in comparative test No. 4, with the difference that the number of volunteers was raised to 11.

The conventional not retarded capsules both together showed the conventional picture of the mean curve 25 in Fig. 8, the drug was released within 10 hours.

The enteric coated retarded tablet of example 12 produced a mean plasma level between 2.5 and 0.8 ng ml of compound B (mean curve 26) from 3 to 28 hours after administration and had an undiminished relative bioavailability, is compared with the conventional capsules .

The enteric coated retard tablet of example 12 makes a once-a-day administration possible, whereas the c nventional capsule has to be taken regularly 2 to 3 times a day.

Example 13 (−)-(S)-4-(2,1,3-benzoxadiazol-4- yl)-1,4-dihyrdo-5-methoxycarbonyl-1-,2,6-trimethyl- 3-pyridine-carboxylic-acid isopropylester (compound C)

In an analogous manner as is described in the examples 1 and 7, a 20, 30, 40 and 50% dispersion of compound C in polyethylene glycol 6000 was preapred.

Of the obtained dispersion granulates which contained 50 mg of compound C, the dissolution rate was determined in an aqueous medium according to the Rotating-Paddle- Method (USP XX).

	Dispersion granulate			
Time in hours	*20%*	*30%*	*40%*	*50%*
0	0	0	0	0
2	100	86	54	27
3		88	60	33
4		88	63	38
5		89	68	44
6		90	72	48

Nifedipine

Example 14

In an analogous manner as is described in examples 1 and 7 a 20% and a 40% dispersion of Nifedipine in polyethylene glycol 6000 was prepared.

Of the obtained dispersion granulates containing 50 mg Nifedipine the dissolution rates were determined in an aqueous medium according to the Rotating-Paddle- Method (USP XX).

	Dispersion granulate	
Time in hours	*20%*	*40%*
0	0	0
2	5	0
3	29	11
4	56	20
5	77	31
6	90	41
7	96	46
8	97	51
12	98	63
16	99	72
20	101	79

CLAIMS

1. A solid dispersion of a pharmacologically active agent in a crystalline matrix as a carrier, in which the active agent

a. has a maximum solubility of 0.01% at 37 C in water,

b. is present in the matrix at a total concentration of above 5 percent by weight, and

c. is present in the matrix at a concentration of above 5 percent by weight in a coherent crystalline form.

2. A dispersion according to claim 1 wherein the active agent is a dihydropyridine.

3. A dispersion according to claim 2 wherein the active agent is a 1,4-dihydro-3,5-dicarboxylic acid diester-2,6-dimethyl-pyridine.

4. A dispersion according to claim 1 wherein the active agent has an optionally substituted 4-phenyl- or a 4-phenyl derivative group.

5. A dispersion according to claim 4 wherein the active agent has a 2,1,3-benzoxadiazol-4-yl group.

6. A dispersion according to claim 5, containing the 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-ethoxy-2,6-dimethyl-3-pyridinecarboxylic acid ethylester as active agent.

7. A dispersion according to claim 5, containing the 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5- methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic acid isopropylester as active agent.

8. A dispersion according to any one of claims 1 to 7, wherein the matrix is a polyalkyleneglycol.

9. A dispersion containing 4-(2,1,3-benzoxadiazol- 4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic acid ethylester as active agent in a polyalkylene glycol matrix.

10. A dispersion containing 4-(2,1,3-benzoxadiazol- 4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3- pyridine carboxylic acid isopropylester as active agent in a polyalkylene glycol matrix.

11. A dispersion according to any one of claims 1 to 10 in a poly(C, ,)alkylene glycol matrix.

12. A dispersion according to claim 11 in a polyethylene glycol.

13. A dispersion according to claim 12 in a polyethylene glycol having a molecular weight from 100 to 20.000.

14. A dispersion according to any one of claims 1 to 13 having above 5 percent by weight of crystalline active agent particles of a diameter of up to 5 micrometres.

15. A dispersion according to claim 14, containing additionally entrapped active agent particles of a diameter of up to 100 micrometres.

16. A dispersion according to any one of claims 1 to 15, containing up to 80 percent of weight of active agent.

17. A dispersion according to any one of claims 1 to 16 in a granulate form.

18. A dispersion granulate according to claim 17, having a diameter of up to 2000 micrometres per granulate particle.

19. A secondary structure of an active agent, obtained from the solid dispersion according to any one of claims 1 to 18, by selective removal of the matrix material.

20. A secondary active agent structure, obtainable from the solid dispersion according to any one of claims 1 to 18 after removal of the matrix material with an aqueous medium.

21. A secondary active agent structure according to claim 19 or 20, irregularly penetrated by fissure-like channels and containing small pores having a diameter of below 5 micrometre.

22. A secondary active agent structure having a surface of 1 to 15 m²/g thereof, measured according to the BET-method and having a pore volume of 20 to 95%, measured by mercury-porosimetry.

23. A pharmaceutical composition containing a dispersion or a structure according to any one of claims 1 to 22.

24. A pharmaceutical composition according to any one of claims 1 to 18, in the form of a tablet.

25. A pharmaceutical composition according to any one of claims 1 to 23, in the form of a capsule.

26. A pharmaceutical composition according to any one of claims 23 to 25, in enteric coated form.

27. A pharmaceutical composition according to any one of claims 23 to 25, containing a solid dispersion and a fatty acid glycerol ester therein.

28. A pharmaceutical composition according to any one of claims 23 to 27 for oral administration once a day, in unit dosage form containing up to 250 mg of active agent.

29. A pharmaceutical composition for oral administration once a day, containing a therapeutically effective amount of 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro- 5-ethoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid ethylester as an active agent.

30. A pharmaceutical composition for oral administration once a day containing a therapeutically effective amount of 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro- 5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester as an active agent.

31. A pharmaceutical composition according to claim 29 capable of producing on administration orally a plasma level of 2 to 8 ng of active agent ml for at least 22 hours, in the event that it contains one dose of 50 mg of 4-(2,1,3-benzoxadiazol-4-yl)-1,4- dihydro-5-ethoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid ethylester as active agent.

32. A pharmaceutical composition according to claim 30 capable of producing on administration orally a plasma level of 1 to 2.5 ng of active agent ml for at least 22 hours, in the event that it contains one dose of 10 mg of 4-(2,1,3-benzoxadiazol-4-yl)-1,4- dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid isopropylester as active agent.

33. A dispersion, a secondary active agent structure or a composition thereof, substantially as hereinbefore described with reference to any one of the examples.

34. A method for the sustained release of an active agent in a pharmaceutical composition by administering the pharmaceutical composition according to any one of the claims 23 to 32.

35. A process for the preparation of a solid dispersion of a pharmacologically active agent in a crystalline matrix as a carrier, characterized in that an active agent having a maximum solubility of 0.01% in water at 37 C, is dissolved at a concentration of above 5 percent by weight in a liquified matrix and the obtained mixture is transformed to a solid form and the active agent is crystallised.

36. A process for the preparation of a pharmaceutical composition, characterized in that the product of the process according to claim 35 is reduced to granulate particle form and is formulated into tablets or capsules as unit dosage forms.

37. A process for the preparation of a secondary structure of an active agent, characterized in that the product of the process according to claim 35 is reduced to granulate particle form and the matrix material is selectively removed.

38. A process for the preparation of a pharmaceutical composition, characterized in that the product of the process according to claim 37 is encapsulated in capsules.

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